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NEWS	5	DEC 14	2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
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NEWS	7	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS	8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS	9	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS	10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS	11	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS	12	JAN 17	IPC 8 in the WPI family of databases including WPIFV

NEWS EXPRESS JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
http://download.cas.org/express/v8.0-Discover/

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FILE 'HOME' ENTERED AT 15:17:28 ON 23 JAN 2006

=> file reg
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION

FULL ESTIMATED COST 0.21 0.21

FILE 'REGISTRY' ENTERED AT 15:17:50 ON 23 JAN 2006

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* available and contains the CA role and document type information. *
*                                                                    *
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```
=> KMD-3213
             8 KMD
          1931 3213
L1           2 KMD-3213
                 (KMD(W)3213)

=> d scan

L1   2 ANSWERS   REGISTRY  COPYRIGHT 2006 ACS on STN
IN   1H-Indole-7-carboxamide, 2,3-dihydro-1-(3-hydroxypropyl)-5-[(2R)-2-[[2-[2-
     (2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-, dihydrobromide (9CI)
MF   C25 H32 F3 N3 O4 . 2 Br H

Absolute stereochemistry.  Rotation (-).
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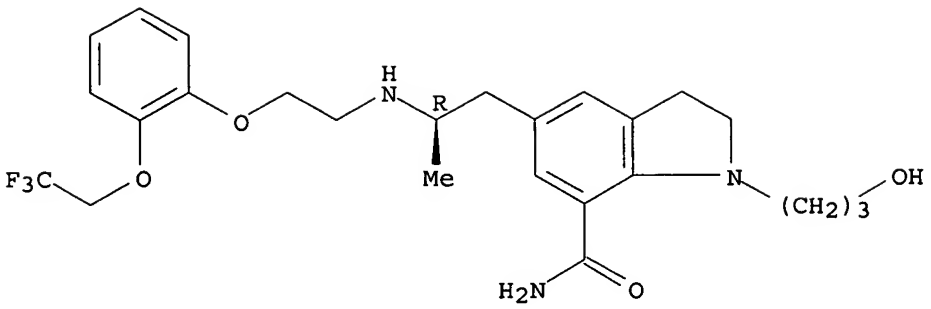
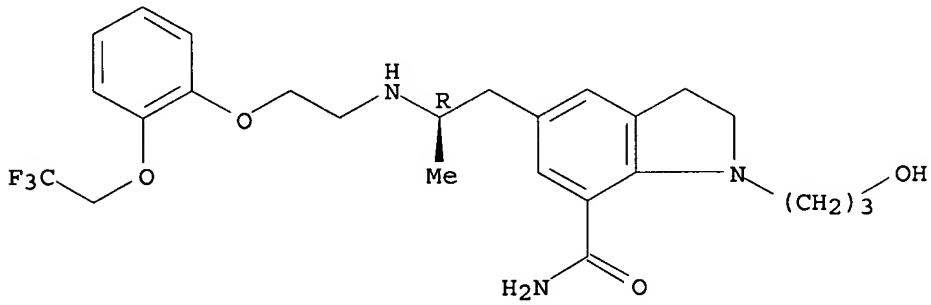


●2 HBr

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L1 2 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 1H-Indole-7-carboxamide, 2,3-dihydro-1-(3-hydroxypropyl)-5-[(2R)-2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]- (9CI)
MF C25 H32 F3 N3 O4
CI COM

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> file caplus medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	11.72	11.93

FILE 'CAPLUS' ENTERED AT 15:20:41 ON 23 JAN 2006
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FILE 'MEDLINE' ENTERED AT 15:20:41 ON 23 JAN 2006

```
=> l1
L2          61 L1

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           61 DUP REM L2 (0 DUPLICATES REMOVED)

=> l3 and PY<2004
L4          41 L3 AND PY<2004

=> d ibib abs 1-41

L4   ANSWER 1 OF 41  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2005:325693  CAPLUS
DOCUMENT NUMBER:         142:379396
TITLE:                   Ophthalmic formulations including selective alpha 1
                         antagonists
INVENTOR(S):             Horn, Gerald
PATENT ASSIGNEE(S):      USA
SOURCE:                  U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of U.S.
                         Ser. No. 854,414.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  6
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     US 2005080056         A1    20050414    US 2004-867144          20040614
     US 6291498            B1    20010918    US 2000-662945          20000915 <--
     US 6730065            B1    20040504    US 2000-675988          20000929
     US 6420407            B1    20020716    US 2000-710758          20001108 <--
     US 2002082288         A1    20020627    US 2001-854414          20010510 <--
     US 2002187986         A1    20021212    US 2002-165459          20020607 <--
     US 6515006            B2    20030204
     WO 2005123093         A2    20051229    WO 2005-US19706         20050603
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,
             NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
             SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
             ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 1999-154033P     P  19990916
                                          US 1999-154893P     P  19990920
                                          US 2000-662945      A2 20000915
                                          US 2000-675988      A2 20000929
                                          US 2000-705526      A2 20001103
                                          US 2000-710758      A2 20001108
                                          US 2001-854414      A2 20010510
                                          US 2000-676988      A2 20001002
                                          US 2000-245868P     P  20001103
                                          US 2004-867144      A  20040614
```

AB The ophthalmic formulations include one or more active agents that act to optimize pupil light reflex while minimizing, or effectively eliminating, any undesired eye redness in response to application thereof. The active agents include, for example, α-1 antagonists, such as α-1a selective antagonists. Phentolamine eye drops were formulated and administered to patients to demonstrate the effectiveness of the invention.

L4 ANSWER 2 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:100815 CAPLUS
DOCUMENT NUMBER: 142:347838
TITLE: Pharmacokinetics and in vivo receptor binding characteristics of α1-adrenoceptor antagonists to treat urinary obstruction in patients with benign prostatic hyperplasia
AUTHOR(S): Okura, Takashi; Yamada, Shizuo; Kimura, Ryohei
CORPORATE SOURCE: Department of Biopharmacy, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, 422-8526, Japan
SOURCE: Recent Research Developments in Drug Metabolism & Disposition (**2002**), 1, 101-115
CODEN: RRDDAQ
PUBLISHER: Transworld Research Network
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The characterization of drug-receptor binding in relation to the pharmacokinetics would provide more practical information to clarify in vivo pharmacol. effects in the development of novel drugs. In this article, we have reviewed the drug disposition and in vivo receptor binding of typical and novel α1-adrenoceptor antagonists (prazosin, tamsulosin, KMD-3213 and JTH-601) to treat urinary obstruction in patients with benign prostatic hyperplasia (BPH), in rat tissues including the prostate, in relation to their pharmacokinetics and pharmacodynamics. It has been shown that there are considerable differences in the plasma pharmacokinetics, in the tissue concentration and in the in vivo α1-adrenoceptor binding characteristics of [3H]prazosin, [3H]tamsulosin,. [3H]KMD-3213 and [3H]JTH-601 in rat tissues after the i.v. injection of these radioligands. Compared with that of [3H]prazosin, the AUC value for plasma free concentration (AUCfree) of [3H]tamsulosin after the i.v. injection in rats was two times greater but the AUCfree value of [3H]KMD-3213 was two times less. [3H]Tamsulosin, [3H]KMD-3213 and [3H]JTH-601 exhibited considerably higher affinity for the prostate α1-adrenoceptors than [3H]prazosin, under in vivo condition. Further, the in vivo receptor binding (extent and time course) of these α1-adrenoceptor antagonists in the rat prostate correlated closely with their pharmacol. effect in the lower urinary tract. Consequently, the data with the disposition and in vivo receptor binding of α1-adrenoceptor antagonists in tissues would be very useful in predicting or characterizing their pharmacol. specificity (potency, duration, receptor subtype specificity and tissue selectivity) in relation to their pharmacokinetics.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:103876 CAPLUS
DOCUMENT NUMBER: 141:184577
TITLE: Constructing biophore of uroselective α1-adrenoceptor antagonist

AUTHOR(S): Fang, Hao; Lu, Jing-fen; Xia, Lin
CORPORATE SOURCE: State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing, 100083, Peop. Rep. China
SOURCE: Journal of Chinese Pharmaceutical Sciences (**2003**), 12(4), 188-191
CODEN: JCHSE4; ISSN: 1003-1057
PUBLISHER: Journal of Chinese Pharmaceutical Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aim: The biophore of uroselective α1-adrenoceptor antagonist was studied by using Apex-3D software on an O2 Silicon Graphics Computer Station. Methods: Five known antagonists (Indoramin, GG-818, RS100975, R-YM12167, and, KMD-3213), which possess both good selectivity and high affinities to prostate and α1-AR subtype, were chosen, for building the biophore. Using an automatic filtering software for obtaining reasonable biophores, the filter parameters were selected: P (probability) >0.8, active (number of active compds.) ≥4, and size (descriptor center) ≥3. Results: Three biophores conformed to the requirements, each of whom contained a basic center, an aromatic ring center and H-site according to the structure-activity relationships of known α1-adrenoceptor antagonist. Conclusion: The biophore model developed by computer simulation with Apex-3D software can be used to design and synthesize a new α1-adrenoceptor antagonist with high activity and low side effect.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:913005 CAPLUS
DOCUMENT NUMBER: 139:391384
TITLE: Use of inhibitors of EGFR-mediated signal transduction for the treatment of benign prostatic hyperplasia (BPH)/prostatic hypertrophy
INVENTOR(S): Singer, Thomas; Colbatzky, Florian; Platz, Stefan
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003094921	A2	20031120	WO 2003-EP4606	20030502 <--
WO 2003094921	A3	20040318		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10221018	A1	20031127	DE 2002-10221018	20020511 <--
CA 2483590	AA	20031120	CA 2003-2483590	20030502 <--
EP 1505981	A2	20050216	EP 2003-727422	20030502

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2005526123	T2	20050902	JP 2004-503006		20030502
US 2003225079	A1	20031204	US 2003-431699		20030508 <--
PRIORITY APPLN. INFO.:			DE 2002-10221018	A	20020511
			US 2002-389815P	P	20020618
			WO 2003-EP4606	W	20030502

OTHER SOURCE(S): MARPAT 139:391384

AB The invention discloses the use of EGF-receptor antagonists for the production of a medicament to prevent and/or treat benign prostatic hyperplasia and/or prostatic hypertrophy, as well as a method for the treatment or prevention of benign prostatic hyperplasia/prostatic hypertrophy involving the administration of an EGF-receptor antagonist, optionally in combination with known compds. for the treatment of benign prostatic hyperplasia/prostatic hypertrophy, and the corresponding pharmaceutical compns. Compds. of the invention include e.g. quinazoline derivs. and monoclonal antibodies. Preparation of 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(N-(2-methoxyethyl)-N-methylamino)-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline is described.

L4 ANSWER 5 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:219664 CAPLUS
DOCUMENT NUMBER: 138:226783
TITLE: Transdermal device containing an indolinecarboxamide for the treatment of urinary tract disorders
INVENTOR(S): Dressen, Frank; Schacht, Dietrich; Wolff, Hans-Michael
PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany; Kissei Pharmaceutical Co., Ltd.
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1293198	A1	20030319	EP 2001-121687	20010914 <--
EP 1293198	B1	20050209		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

AT 288745	E	20050215	AT 2001-121687	20010914
PT 1293198	T	20050630	PT 2001-121687	20010914
ES 2237515	T3	20050801	ES 2001-1121687	20010914
WO 2003024432	A2	20030327	WO 2002-EP10229	20020912 <--
WO 2003024432	A3	20030904		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

HK 1054327	A1	20050729	HK 2003-106545		20030911
US 2005226919	A1	20051013	US 2004-497199		20040528
PRIORITY APPLN. INFO.:			EP 2001-121687	A	20010914

WO 2002-EP10229 W 20020912

OTHER SOURCE(S): MARPAT 138:226783

AB A transdermal device (TTS) for the administration of an indolinecarboxamide such as KMD 3213. The TTS is efficient in the treatment of urinary tract disorders, such as benign prostatic hypertrophy. Thus, 1 g KMD-3213 was dissolved in 8 g EtOH 1 g oleic acid. A solution (32.1 g) containing 18 g DuroTak 387-2287 in EtOAc was added to the above mixture and the mixture stirred until a homogeneous dispersion was obtained. The dispersion was coated onto a polyester release liner (Scotchpak-1022) and the solvents were removed in a drying oven at a temperature of 50° for about 30 min to obtain an adhesive 40 matrix of 76g/m2 coating weight, which contained 5% drug. The dried matrix film was laminated with a polyester type backing foil (Scotchpak-1109). The individual patches were punched out of the complete laminate to a desired patch size (for example 5, 10, 20, 30 cm2) and sealed into pouches under the flow of nitrogen. The patches obtained were studied by using several test methods.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:69926 CAPLUS

DOCUMENT NUMBER: 139:30476

TITLE: Systemic α1A-adrenoceptor antagonist inhibits neointimal growth after balloon injury of rat carotid artery

AUTHOR(S): Teeters, John C.; Erami, Cauveh; Zhang, Hua; Faber, James E.

CORPORATE SOURCE: Department of Cell and Molecular Physiology, University of North Carolina, Chapel Hill, NC, 27599-7545, USA

SOURCE: American Journal of Physiology (2003), 284(1, Pt. 2), H385-H392
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous in vitro and in vivo studies have shown that norepinephrine, acting through α1A-adrenoceptors, stimulates hypertrophy, proliferation, and migration of vascular smooth muscle cells and adventitial fibroblasts and may contribute to neointimal growth, lumen loss, and inward remodeling caused by iatrogenic wall injury and vascular disease. Our present aim was to determine whether i.v. administration of the α1A-adrenoceptor antagonist KMD-3213, at dosages without systemic hemodynamic effects, inhibits wall growth after injury. Inhibition of α1A-adrenoceptors with 12.8 and 32 μg/kg KMD-3213 had no effect on arterial pressure or renal and hindquarter resistances in anesthetized rats. A second group then received carotid balloon injury and continuous i.v. KMD-3213 at 4 and 10 μg·kg 1·h-1 for 2 wk. Mean, systolic, and diastolic arterial pressures and heart rate of conscious unrestrained rats were unaffected. KMD-3213 reduced neointima growth by .apprx.30 and 46% at the two doses ($P < 0.01$). These data support the novel hypothesis that a direct α1A-adrenoceptor-dependent trophic action of catecholamines is augmented by injury and may contribute significantly to hypertrophic vascular disease.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:834474 CAPLUS
DOCUMENT NUMBER: 138:331604
TITLE: Effects of KMD-3213, a uroselective α1A-adrenoceptor antagonist, on the tilt-induced blood pressure response in normotensive rats
AUTHOR(S): Akiyama, Katsuyoshi; Hora, Masachiyo; Yamagishi, Ryoichi; Kitazawa, Makio
CORPORATE SOURCE: Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., Nagano, 399-8304, Japan
SOURCE: Japanese Journal of Pharmacology (2002), 90(2), 131-137
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB KMD-3213 ((-)-1-(3-hydroxypropyl)-5-((2R)-2-{[2-({2-[(2,2,2-trifluoroethyl)oxy]phenyl}oxy)ethyl]amino}propyl)-2,3-dihydro-1H-indole-7-carboxamide), an α1A-adrenoceptor antagonist with potency similar to that of tamsulosin, is under development for the treatment of bladder outlet obstruction in patients with benign prostatic hypertrophy. In the present study, we investigated the effects of KMD-3213 on the tilt-induced blood pressure response in anesthetized normotensive rats. Male normotensive Sprague-Dawley rats were placed in the supine position on a board under cocktail anesthetization (α-chloralose, urethane and sodium pentobarbital). The arterial blood pressure was measured from the carotid artery. The animals were given consistent 45° head-up tilt from the horizontal position, following the transient decrease in the blood pressure, and then recovery of the blood pressure to the normal level. Significant orthostatic hypotension was seen with i.v. administration of both prazosin and tamsulosin at doses over 3 μg/kg, and these drugs completely blocked the tilt-induced blood pressure responses at 30 μg/kg. On the other hand, these responses were still retained when KMD-3213 was administered i.v. at a dose up to 75 μg/kg of KMD-3213. Moreover, KMD-3213 showed the highest uroselectivity of the test drugs. These results indicate that KMD-3213 is not likely to induce orthostatic hypotension and would be a useful compound for the treatment of urinary outlet obstruction in patients with benign prostatic hyperplasia.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:755212 CAPLUS
DOCUMENT NUMBER: 137:279361
TITLE: Preparation of nitrosated and nitrosylated α-adrenergic receptor antagonists for the treatment of sexual dysfunction
INVENTOR(S): Garvey, David S.; Saenz De Tejada, Inigo; Gaston, Ricky D.; Khanapure, Subhash P.; Shelekhin, Tatiana E.; Wang, Tiansheng
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 61 pp., Cont.-in-part of U.S. 6,294,517.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2002143007	A1	20021003	US 2002-146671		20020516 <--
US 5932538	A	19990803	US 1996-595732		19960202 <--
US 5994294	A	19991130	US 1996-714313		19960918 <--
US 6294517	B1	20010925	US 1998-145143		19980901 <--
US 2005187222	A1	20050825	US 2005-109761		20050420
PRIORITY APPLN. INFO.:			US 1996-595732	A2	19960202
			US 1996-714313	A2	19960918
			US 1998-145143	A2	19980901
			WO 1997-US1294	A2	19970128
			US 1999-387724	A1	19990901
			US 2002-146671	A1	20020516

OTHER SOURCE(S): MARPAT 137:279361
GI

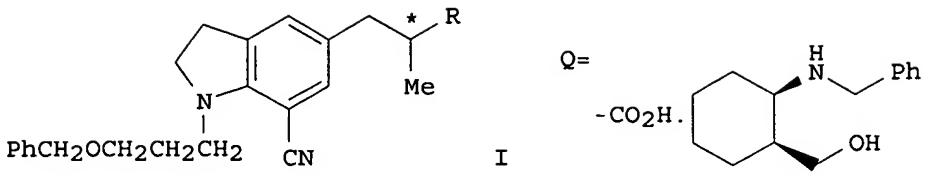
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I, II, III, etc. [R1 = H, alkoxy; R2 = NMe(CH2)aNHCORc, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl, etc.; a= 2, 3; Rc = heterocyclic, alkyl, hydroxyalkyl, etc.; D = NO, NO2, etc.; R3 = CH2N(4-MeC6H4)(3-DOC6H4), CH2Ph, 2-methoxy-1,4-benzodioxin-2-yl, etc.; D1 = H or D with the proviso that D1 must be D if there is no other D in the compound; R4 = H, D, CORd; R5 = H, C(O)ORk, etc.; Rd = H, alkyl, cycloalkyl, etc.; Rk = H, alkyl] were prepared For example, nitrosylation of thiol IV (X = H), e.g., prepared from 4-[2-(dimethylamino)ethoxy]-2-methyl-5-(methylethyl)phenyl acetate in 3-steps, with NaNO2/HCl afforded IV.HCL (X = NO) in 82% yield. Compds. I, II, III, etc., donate, transfer or release nitric oxide or elevate levels of endogenous endothelium-derived relaxing factor, and are useful for treatment of sexual dysfunctions in males and females. In erectile response of anesthetized rabbits (2.5 kg), S-nitrosoglutathione, e.g., prepared from glutathione and NaNO2/HCl, at 500 μg dosage was able to induce near maximal response relative to the standard dose of pap/phent/PGE1.

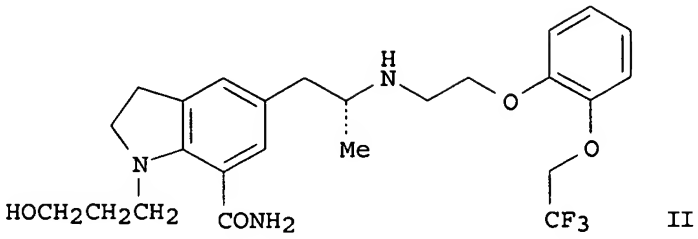
L4 ANSWER 9 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:708796 CAPLUS
DOCUMENT NUMBER: 137:232552
TITLE: Preparation of 1-(3-benzyloxypropyl)-5-(2-substituted propyl)indolines as intermediates for drug for treating dysuria
INVENTOR(S): Yamaguchi, Toshiaki; Takeuchi, Hideki; Shiohara, Hiroaki
PATENT ASSIGNEE(S): Kissei Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002265444	A2	20020918	JP 2001-65686	20010308 <--
PRIORITY APPLN. INFO.:			JP 2001-65686	20010308

OTHER SOURCE(S): CASREACT 137:232552; MARPAT 137:232552
GI



I



II

AB The title compds. (I; R = CO2H, CONH2, NH2; Q; the carbon atom denoted by * represents the carbon atom with R or RS configuration; provided that the carbon atom denoted by * represents the carbon atom with R configuration, R is CO2H) are prepared These compds. are useful as intermediates for (R)-1-(3-hydroxypropyl)-5-[2-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino]propyl]indoline-7-carboxamide (II) which possesses selective smooth muscle relaxant activity for urinary tract and little effect on blood pressure and is useful as a therapeutic agent for dysuria. Thus, 2.00 g 3-[1-(3-benzyloxypropyl)-7-cyanoindolin-5-yl]-2-methylpropionic acid (III) and 11.6 g (1S,2R)-cis-(-)-2-benzylaminocyclohexanemethanol (IV) were dissolved in 100 mL EtOAc with heating, stirred with 1.0 g activated charcoal at room temperature for 30 min, and filtered. To the filtrate was added portionwise 100 mL hexane, followed by seeding with a diastereomer salt prepared sep., and the resulting mixture was stirred overnight at room temperature and filtered to give, after washing the crystals with hexane/EtOAc (2/1) and drying at 50 ° for 3 h, the diastereomer salt (13.4 7 g). The diastereomer salt was recrystd. from hexane/EtOAc to give 5.99 g (R)-III.IV (92.8% ee) which (5.00 g) was stirred with 50 mL 1 M aqueous HCl and 50 mL EtOAc at for 1 h and the EtOAc layer was separated, washed with aqueous NaCl, and dried over anhydrous Na2SO4, followed by distilling off th solvent to give 3.20 g (R)-III (91.8% ee). To a solution of 3.00 g (R)-III in MeCN was added 2.57 g 1,1'-carbonyldiimidazole and stirred at room temperature overnight, treated with a saturated NH3 solution in MeCN (20 mL), sealed, and stirred overnight to give 2.83 g (R)-3-[1-(3-benzyloxypropyl)-7-cyanoindolin-5-yl]-2-methylpropionamide (V). To a solution of 1.00 g V in 15 mL isopropanol was added 14 mL 15% aqueous NaOCl at room temperature, followed by adding 7 mL 2 M aqueous NaOH under ice-cooling, and the resulting mixture was stirred at 40° for 1 h to give 0.915 g (R)-5-(2-aminopropyl)-1-(3-benzyloxypropyl)indoline-7-carbonitrile (VI). To a solution of 0.80 g VI in 8 mL tert-butanol were added 0.291 g Na2CO3 and 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl trifluoromethanesulfonate and refluxed overnight to give 0.564 g (R)-1-(3-benzyloxypropyl)-5-[2-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino]propyl]indoline-7-carbonitrile which (0.50 g) was dissolved in 5 mL MeCN, stirred at room temperature with 0.135 mL

30% aqueous H2O2 and 0.054 mL 5 M aqueous NaOH overnight and then with 0.100 mL 30% aqueous H2O2 and 0.100 mL 5 M aqueous NaOH for 5 h to give 0.391 g (R)-1-(3-benzyloxypropyl)-5-[2-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino]propyl]indoline-7-carboxamide (VII). A solution of 0.35 g VII in 3 mL ethanol was treated with 1.44 mL 1 M aqueous HCl and 0.060 g 10% Pd-C and stirred under hydrogen atmospheric for 3 h to give 0.207 g II.

L4 ANSWER 10 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:701974 CAPLUS
DOCUMENT NUMBER: 138:395429
TITLE: Identification of binding sites of prazosin, tamsulosin and KMD-3213 with α1-adrenergic receptor subtypes by molecular modeling
AUTHOR(S): Ishiguro, Masaji; Futabayashi, Yukiyo; Ohnuki, Toshio; Ahmed, Maruf; Muramatsu, Ikunobu; Nagatomo, Takafumi
CORPORATE SOURCE: Suntory Institute for Bioorganic Research, Shimahon-cho, Mishima-gun, Osaka, 618-8503, Japan
SOURCE: Life Sciences (2002), 71(21), 2531-2541
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This investigation was performed to assess the importance of interaction in the bindings of selective and nonselective α1-antagonists to α1-adrenergic receptor (α1-AR) subtypes using mol. modeling. The α1-antagonists used in this study were prazosin, tamsulosin and KMD-3213. Mol. modeling was performed on Octane 2 workstation (Silicon Graphics) using Discover/Insight II software (Mol. Simulations Inc.). Through mol. modeling, possible binding sites for these drugs were suggested to lie between transmembrane domains (TM) 3, 4, 5 and 6 of the α1-AR subtypes. In prazosin, the 4-amino group, 1-nitrogen atom and two methoxy groups of quinazoline ring possibly interact with the amino acids in TM3, TM5 and TM6 of α1-ARs. In tamsulosin, amine group of ethanyl amine chain, methoxy group of benzene ring and sulfonamide nitrogen of benzene ring interacts in TM3, TM4 and TM5 of α1-ARs. In KMD-3213, amine of Et amine chain and indoline nitrogen of this compound possibly interact within TM3 and TM5 of α1-ARs. Amide nitrogen of KMD-3213 also interacts within TM4 of α1A-AR. The results of the present study suggested that prazosin has similar binding sites in all the α1-AR subtypes while tamsulosin interacts at higher number of sites with α1D-subtype than other α1-AR subtypes. KMD-3213 being an α1A-AR selective ligand, binds to higher number of sites of α1A subtype than to other subtypes. All these amino acids are located near the extracellular loop. These findings are consistent with the previous studies that antagonists bind higher in the pocket closer to the extracellular surface unlike agonist binding.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:584872 CAPLUS
DOCUMENT NUMBER: 138:147436
TITLE: Selective and sustained occupancy of prostatic α1-adrenoceptors by oral administration of KMD-3213 and its plasma concentration in rats
AUTHOR(S): Okura, T.; Yamada, S.; Abe, Y.; Kimura, R.
CORPORATE SOURCE: Department of Biopharmacy, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, 422-8526, Japan
SOURCE: Journal of Pharmacy and Pharmacology (2002),

54(7), 975-982
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Pharmaceutical Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study examined the ex-vivo occupancy by KMD-3213 of α1-adrenoceptors in the prostate and other tissues of rats in terms of tissue selectivity and duration of occupancy in relation to plasma concentration Oral administration of KMD-3213 (0.2-20.2 μmol kg-1, 0.5 h) dose-dependently decreased [3H]prazosin binding sites (Bmax) in the prostate (42-74%) and submaxillary gland (54-88%) compared with the control value. In contrast, there was only a slight change in the Bmax values in the spleen and cerebral cortex of KMD-3213-treated rats. The α1-adrenoceptor occupancy in the prostate and submaxillary gland was increased, with plasma free concentration of KMD-3213 at 0.5 h after oral administration of KMD-3213 (0.6-20.2 μmol kg-1). The receptor occupancy in these tissues was much greater than that in the spleen, heart or cerebral cortex. After oral administration of KMD-3213 (6.1 μmol kg-1), the α1-adrenoceptor occupancy in the prostate and submaxillary gland occurred rapidly, in parallel with the rise in the plasma concentration of the drug, and it lasted for at least 24 h, despite a remarkable decrease in the plasma concentration It is concluded that KMD-3213 may produce fairly selective and sustained occupancy of α1-adrenoceptors in the prostate, a target organ for treatment of bladder outlet obstruction in patients with benign prostatic hyperplasia.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:322954 CAPLUS
DOCUMENT NUMBER: 137:210832

TITLE: Alpha-1 adrenoceptor up-regulation induced by prazosin but not KMD-3213 or reserpine in rats

AUTHOR(S): Zhang, Li; Taniguchi, Takanobu; Tanaka, Takashi; Shinozuka, Kazumasa; Kunitomo, Masaru; Nishiyama, Masahiko; Kamata, Koji; Muramatsu, Ikunobu
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Fukui Medical University, Fukui, 910-1193, Japan

SOURCE: British Journal of Pharmacology (2002), 135(7), 1757-1764
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have investigated the effects of chronic administration of prazosin (a subtype-nonspecific alpha-1 AR antagonist), KMD-3213 (an alpha-1A AR subtype-specific antagonist) and reserpine (a catecholamine depletor) on the d. of alpha-1 AR subtypes in various rat tissues (liver, kidney, submaxillary gland, heart and spleen). Administration of prazosin (2 mg kg-1 day-1, i.p.) for 2 wk did not affect KD values for [3H]-prazosin or [3H]-KMD-3213 of alpha-1 ARs in five rat tissues tested. However, it caused 52% up-regulation of alpha-1B AR in the spleen, and 84% and 107% up-regulation of alpha-1A- and alpha-1B ARs, resp., in the heart. Although major subtypes of alpha-1 AR are alpha-1A AR in the submaxillary gland, alpha-1B AR in the liver, and alpha-1A and alpha-1B ARs in the kidney, these tissues showed no up-regulation. The mRNA levels of alpha-1 AR subtypes were not affected by prazosin administration in any tissue tested. Neither administration of KMD-3213 (2 mg kg-1 day-1, i.p.) nor reserpine (0.5-1 mg kg-1 day-1, i.p.) for 2 wk caused any change in either the binding affinity for [3H]-prazosin or [3H]-KMD-3213 or the d. of the

alpha-1 AR subtypes in the five rat tissues. Neither prazosin nor KMD-3213 treatment reduced the noradrenaline content in the five rat tissues, in contrast to reserpine treatment, which markedly reduced it. The findings of the present study demonstrated that up-regulation of alpha-1 AR is selectively caused by prazosin treatment in some tissues but neither by KMD-3213 treatment nor by chemical denervation with reserpine. These results suggest that up-regulation of alpha-1 ARs is not caused by a simple blockade of sympathetic tone.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:316314 CAPLUS
DOCUMENT NUMBER: 137:41995
TITLE: Differences in the subcellular localization of α1-adrenoceptor subtypes can affect the subtype selectivity of drugs in a study with the fluorescent ligand BODIPY FL-prazosin
AUTHOR(S): Sugawara, Tatsuo; Hirasawa, Akira; Hashimoto, Keitaro; Tsujimoto, Gozoh
CORPORATE SOURCE: Department of Molecular, Cell Pharmacology, National Children's Medical Research Center, Tokyo, 154, Japan
SOURCE: Life Sciences (2002), 70(18), 2113-2124
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB G protein-coupled receptor (GPCR) subtypes are differentially distributed in the cell; however, it remains unclear how this affects the subtype selectivity of particular drugs. In the present study, we used flow cytometry anal. with the fluorescent ligand, BODIPY FL-prazosin, to study the relationship between the subcellular distribution of subtype receptors and the subtype-selective character of ligands using α1a- and α1b-adrenoceptors (ARs). α1a-ARs predominantly localize inside the cell, while α1b-ARs on the cell surface. Flow cytometry anal. and confocal laser-scanning micrographs of living cells showed that BODIPY FL-prazosin can label not only α1-ARs on the cell surface, but also those localized inside the cell. Furthermore, flow cytometry anal. of α1A-AR-selective drug, KMD-3213, and α1B-AR-selective drug, CEC, revealed that the major determinant of the subtype selectivity of each drug is different. The α1A-AR selectivity of KMD-3213 can be explained by its much higher affinity for α1a-AR than α1b-AR (affinity-dependent selectivity), while the α1B-AR selectivity of the hydrophilic alkylating agent CEC is due to preferential inactivation of α1-ARs on the cell surface (receptor localization-dependent selectivity). This study illustrates that factors in addition to the affinity of the drug for the receptor, such as subcellular localization of the receptor, should be taken into account in assessing the subtype selectivity of a drug.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:141672 CAPLUS
DOCUMENT NUMBER: 137:195277
TITLE: Effects of α1-adrenoceptor blockade on canine ischemia/reperfusion-induced arrhythmias
AUTHOR(S): Katahira, S.; Sugawara, T.; Tsujimoto, G.; Sugiyama, A.; Tada, Y.; Hashimoto, K.
CORPORATE SOURCE: Second Department of Surgery, Yamanashi Medical

University, Yamanashi, 409-3898, Japan
SOURCE: Asia Pacific Journal of Pharmacology (2001), 15(3), 47-56
CODEN: APJPEV; ISSN: 0217-9687
PUBLISHER: Singapore University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study was designed to ascertain whether the selective pharmacol. blockade of α1-receptors prevents arrhythmias during acute myocardial ischemia and reperfusion in beagle dogs. We used a new α1a-adrenoceptor selective blocking drug, KMD-3213 and an α1-blocker, prazosin. A pair of beagles, one received the drug {KMD-3213 0.1 mg/kg, i.v. (n=8) or prazosin 0.5 mg/kg, i.v. (n=8)} and the other, the vehicle was used. The left anterior descending coronary artery (LAD) was ligated 10 min after either drug or vehicle administration. After 30 min, the ligation was released. α1-Adrenergic receptor assay was performed to examine whether acute ischemia alters the number of receptors in the myocardium. The number of dogs which showed ventricular fibrillation (VF) either during ischemia or immediately after reperfusion was 1 in the KMD-3213 treated group, 4 in the corresponding vehicle group, 3 in the prazosin group and 4 in the corresponding vehicle group, resp. The decrease in the incidence of VF in KMD-3213 group became significant when we compared treated group with our cumulated data of control dogs (n=192, $p<0.05$). The receptor assay revealed that the subtype of α1-receptors prominent in the dog heart is α1b and the number of receptor was decreased in the ischemic area. Taking the receptor assay results into consideration, the lack of definite favorable effects of α1-adrenoceptor blockade on canine ischemia/reperfusion-induced arrhythmia can be explained by insufficient block of α1b receptors by the present blockers.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:104436 CAPLUS
DOCUMENT NUMBER: 137:88401
TITLE: Relationship between Prostatic α1-Adrenoceptor Binding and Reduction in Intraurethral Pressure following Continuous Infusion of KMD-3213 in Rats
AUTHOR(S): Akiyama, Katsuyoshi; Tatemichi, Satoshi; Katayama, Susumu; Nakajima, Mariko; Oki, Tomomi; Okura, Takashi; Yamada, Shizuo; Kimura, Ryohei
CORPORATE SOURCE: Pharmacology Research, R&D, Kissei Pharmaceutical Co., Ltd., Matsumoto, Japan
SOURCE: Pharmacology (2002), 64(3), 140-147
CODEN: PHMGBN; ISSN: 0031-7012
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relationship between α1-adrenoceptor binding in rat tissues and pharmacodynamic effects of continuous infusion of KMD-3213 was examined In vivo specific binding of [3H]KMD-3213 after continuous i.v. infusion of the ligand (100 pmol/kg/min for 10 min, followed by 30 pmol/kg/min for 60 or 90 min) differed largely among the tissues examined Specific binding of [3H]KMD-3213 in aorta, heart, lung, and kidney was not different in terms of infusion time in the case of continuous infusion for 10, 70 and 100 min, whereas the binding in prostate, vas deferens, and submaxillary gland by 70- and/or 100-min infusion was significantly greater than that by the 10-min infusion. A similar extent of specific binding in the prostate was observed by the infusion (100 min) of a three-fold higher dose of [3H]KMD-

3213. Continuous i.v. infusion of KMD-3213 (100 pmol/kg/min for 10 min, followed by 30 pmol/kg/min) for 70 or 100 min significantly reduced the phenylephrine-induced increase in the mean blood pressure and that in the intraurethral pressure of anesthetized rats. Extent and time course of the KMD-3213 effect reduction in the phenylephrine-induced increase in intraurethral pressure were closely associated with those in prostatic [3H]KMD-3213 binding after continuous infusion of the corresponding dosage of the radioligand. The reduction in the phenylephrine-induced increase by the infusion of a three-fold higher dose of KMD-3213 was significantly greater in the case of the intraurethral pressure than in that of the mean blood pressure, thereby suggesting a greater selectivity for the α1-adrenoceptor in the lower urinary tract than for that in the vascular tissue. In conclusion, the present study has shown that specific binding of [3H]KMD-3213 in the rat prostate after the continuous i.v. infusion of the radioligand may be closely associated with the pharmacol. effect of this drug on the lower urinary tract.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:755588 CAPLUS
DOCUMENT NUMBER: 135:298817
TITLE: Adrenoceptor antagonists for the treatment of lower urinary tract diseases
INVENTOR(S): Shimoyama, Mitsuru; Watanabe, Takeshi; Kodachi, Naonori
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001288115	A2	20011016	JP 2001-30303	20010207 <--
CA 2435989	AA	20020815	CA 2002-2435989	20020206 <--
WO 2002062390	A1	20020815	WO 2002-JP968	20020206 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1358889	A1	20031105	EP 2002-711333	20020206 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004072851	A1	20040415	US 2003-470550	20030730
PRIORITY APPLN. INFO.:			JP 2001-30303 A	20010207
			WO 2002-JP968 W	20020206

AB This invention relates to the use of α1-receptor blockers for the treatment of lower urinary tract disorders, which include instable bladder, chronic prostatitis, chronic bladder infections, prostatic pain, Hinman syndrome, Fowler syndrome, psychogenic urination disorders, drug-induced urination disorders, or age-related urination disorders. Claimed α1-receptor blockers include naftopidil, alfuzosin,

fiduxosin, upidosin, KMD 3213, SNAP-5089, AIO-8507L, SL-890591, RS-100329, and salts thereof.

L4 ANSWER 17 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:751243 CAPLUS
DOCUMENT NUMBER: 136:111966
TITLE: KMD-3213
AUTHOR(S): Sorbera, L. A.; Silvestre, J.; Castaner, J.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (2001), 26(6), 553-560
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review describing the synthesis, pharmacol. actions, and clin. studies of KMD-3213, a novel α1-adrenoceptor antagonist. This compound has shown highly selective inhibitory activity against α1A-adrenoceptor, which is the predominant receptor in the prostate.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:341407 CAPLUS
DOCUMENT NUMBER: 135:327295
TITLE: Effect of KMD-3213, an α1A-adrenoceptor antagonist, on the prostatic urethral pressure and blood pressure in male decerebrate dogs
AUTHOR(S): Akiyama, Katsuyoshi; Noto, Hiromitsu; Nishizawa, Osamu; Sugaya, Kimio; Yamagishi, Ryoichi; Kitazawa, Makio; Tsuchida, Seigi
CORPORATE SOURCE: Central Research Laboratories, KISSEI Pharmaceutical Co. Ltd, Nagano, 399-8304, Japan
SOURCE: International Journal of Urology (2001), 8(4), 177-183
CODEN: IJURF3; ISSN: 0919-8172
PUBLISHER: Blackwell Science Asia Pty Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB KMD-3213 is an α1A-adrenoceptor-selective antagonist currently being developed for the treatment of urinary outlet obstruction in patients with benign prostatic hyperplasia. In the present study, the uroselectivity of KMD-3213 was evaluated and compared with that of prazosin and tamsulosin in a decerebrate dog model. Intercollicular decerebration was carried out in male mongrel dogs under anesthesia. The inhibitory effects of i.v. and intraduodenally administered compds. on the increase in intraurethral pressure (IUP) induced by elec. stimulation of the hypogastric nerve were estimated Systemic blood pressure was measured simultaneously. The α1-antagonists tested produced a dose-dependent inhibition of the induced IUP response and decreased mean blood pressure (MBP). The ID50 of KMD-3213, tamsulosin and prazosin for IUP (dose required to inhibit the increase in IUP by 50%) was 3.15, 1.73 and 11.8 μg/kg i.v., resp., and the ED20 for the hypotensive effect (dose required to reduce MBP by 20%) was 8.03, 0.59 and 2.46 μg/kg i.v., resp. The data indicate that uroselectivity (ED20/ID50) of KMD-3213 is 12- and 7.5-fold higher than that of prazosin and tamsulosin, resp. When the drugs were administered intraduodenally, KMD-3213 was sufficiently absorbed from the digestive tract and continued to demonstrate at least 3.8-fold higher uroselectivity than tamsulosin. Based on these findings, KMD-3213 appears to be an effective orally active compound for decreasing urethral resistance during micturition that does not induce any neg. cardiovascular effects in

patients with benign prostatic hyperplasia.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:19405 CAPLUS
DOCUMENT NUMBER: 134:260860
TITLE: Biophore development for prostate-selective α1-adrenoceptor antagonist
AUTHOR(S): Fang, Hao; Lu, Jing-fen; Xia, Lin; Zhang, Li-he
CORPORATE SOURCE: Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, 100083, Peop. Rep. China
SOURCE: Jisuanji Yu Yingyong Huaxue (2000), 17(5), 453-456
CODEN: JYYHE6; ISSN: 1001-4160
PUBLISHER: Jisuanji Yu Yingyong Huaxue Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB To establish the biophore of prostate-selective α1-adrenoceptor antagonist. Method: Five compds. were selected with high affinity on α1A-AR and prostate. The structures of each compound were built and further optimized by dynamic methods. Then the systematic searching method was used to seek out a series lower energy conformations. The Apex-3D software identified biophore and the biophores were chosen by the structure-activity relationship of α1-adrenoceptor antagonist. Result: Three biophores conform our demand. Each biophore contains a basic nitrogen atom, an aromatic ring center and a H-site. Conclusion: This will help us design and synthesis of structurally new prostate-selective α1-AR antagonists with higher activity and lower side effect.

L4 ANSWER 20 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:8430 CAPLUS
DOCUMENT NUMBER: 134:217161
TITLE: In vivo demonstration of α1A-adrenoceptor subtype selectivity of KMD-3213 in rat tissues
AUTHOR(S): Yamada, Shizuo; Okura, Takashi; Kimura, Ryohei
CORPORATE SOURCE: Department of Biopharmacy, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 296(1), 160-167
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study was undertaken to characterize the in vivo α1-adrenoceptor binding of KMD-3213, a novel selective antagonist of α1A-adrenoceptors, in rat tissues by using a tritiated ligand with high specific activity, in comparison with that of [3H]prazosin. A significant degree of in vivo specific binding of [3H]KMD-3213 after i.v. injection of the radioligand (1.4 nmol/kg) was seen in most rat tissues, except the cerebral cortex, spleen, and liver, which showed a little or no specific binding. There was a notable difference among tissues in the time course of specific [3H]KMD-3213 binding after i.v. injection of the ligand. The specific binding in the lung, kidney, and spleen was greatest at 10 min and declined rapidly with the disappearance of the ligand from the plasma. On the other hand, [3H]KMD-3213 binding in the submaxillary gland, vas deferens, and prostate attained peak levels at 60 min, and a considerable degree of binding was present even at 240 min. After i.v.

injection of a similar dose (1.2 nmol/kg) of [3H]prazosin in rats, the in vivo specific binding in the submaxillary gland was greatest at 10 min and then it fell rapidly, whereas [3H]prazosin binding in the spleen attained a peak level at 60 min, and this was maintained even at 120 min. The AUC0-120 values of the specific binding for [3H]KMD-3213, compared with those of [3H]prazosin, were markedly lower in the rat aorta, spleen, and liver, whereas the prostate, submaxillary gland, and lung showed significantly higher AUC0-120 values of [3H]KMD-3213 compared with [3H]prazosin. Furthermore, the in vivo specific binding of [3H]KMD-3213 at dose ranges of 1.4 to 13.6 nmol/kg increased linearly in the prostate and submaxillary gland, but did not increase in a dose-dependent manner in the spleen. On the other hand, there was a dose-dependent increase in the in vivo specific binding of [3H]prazosin at doses of 1.2 to 10.6 nmol/kg in all tissues. The in vivo specific binding of [3H]KMD-3213 in rat tissues was reduced by concomitant i.v. injection of low doses of prazosin in a dose-dependent manner, but not by even a relatively high dose of yohimbine. .In conclusion, the present study shows that KMD-3213 binds to the α1A-adrenoceptor subtype with a higher affinity than to the α1B- and α1D-subtypes under in vivo condition, thus leading to prostate selectivity.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:748369 CAPLUS
DOCUMENT NUMBER: 134:36956
TITLE: Inverse agonism and neutral antagonism at a constitutively active alpha-1a adrenoceptor
AUTHOR(S): Zhu, Jun; Taniguchi, Takanobu; Takauji, Rumiko; Suzuki, Fumiko; Tanaka, Takashi; Muramatsu, Ikunobu
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Fukui Medical University, Fukui, 910-1193, Japan
SOURCE: British Journal of Pharmacology (2000), 131(3), 546-552
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have studied the antagonist action of prazosin and KMD-3213 in a constitutively active mutant of the human alpha-1a adrenoceptor in which Ala271 was substituted to Thr and was expressed in CHO cells. Inverse agonism was characterized by up-regulation of receptor d., a decrease in basal GTPγS binding, and a reduction in basal inositol-1,4,5-triphosphate (IP3) level. According to the above criteria, prazosin acted as an inverse agonist, while KMD-3213 behaved as a neutral antagonist. Compared with the wild-type receptor, mutant receptor exhibited single affinity sites for [3H]-prazosin, [3H]-KMD and the non-radioactive ligands tested, and displayed significantly higher affinities for several agonists but not for the two antagonists. Administration of KMD-3213 to prazosin-treated CHO cells expressing the mutant receptor reversed the inverse agonism of prazosin resulting in rapid increases in cellular IP3, in intracellular [Ca2+] and in the rate of extracellular acidification. These results indicated that a neutral antagonist can reverse the action of an inverse agonist at the receptor site. The distinct properties of inverse agonist and neutral antagonist in affecting receptor function may be important for the clin. use of such antagonists.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:631903 CAPLUS
DOCUMENT NUMBER: 133:232852
TITLE: α1A adrenoceptor mutant for determination of antagonist and inverse agonist activity and treatment of urinary incontinence associated with prostate hypertrophy
INVENTOR(S): Muramatsu, Ikunobu; Taniguchi, Takanobu; Murata, Satoshi; Tatsumichi, Satoshi; Akiyama, Katsuyoshi
PATENT ASSIGNEE(S): Kissei Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000247998	A2	20000912	JP 1999-51163	19990226 <--

PRIORITY APPLN. INFO.: JP 1999-51163 19990226

AB α1A adrenoceptor mutant (substitution of alanine (271) by threonine) is used for determination of antagonist and inverse agonist activity and treatment of urinary incontinence associated with prostate hypertrophy. The α1A adrenoceptor antagonist (-)-(R)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide and its pharmacol. acceptable salts are claimed for treatment of urinary incontinence associated with prostate hypertrophy.

L4 ANSWER 23 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:558944 CAPLUS
DOCUMENT NUMBER: 133:276210
TITLE: Tissue selectivity of KMD-3213, an α1-adrenoceptor antagonist, in human prostate and vasculature
AUTHOR(S): Murata, Satoshi; Taniguchi, Takanobu; Takahashi, Masahiko; Okada, Kenichiro; Akiyama, Katsuyoshi; Muramatsu, Ikunobu
CORPORATE SOURCE: Department of Pharmacology and Urology, School of Medicine, Fukui Medical University, Matsuoka, Japan
SOURCE: Journal of Urology (Baltimore) (**2000**), 164(2), 578-583
CODEN: JOURAA; ISSN: 0022-5347
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We evaluated the binding and functional affinity of KMD-3213 and other α1-adrenoceptor (AR) antagonists such as prazosin or tamsulosin, to compare the tissue selectivity of these antagonists between human prostate and vasculature. In the binding expts., saturation expts. using [3H]-KMD and [3H]-prazosin (PZ) were performed, and competition of [3H]-PZ binding by antagonists was also examined in human prostatic and aortic membranes. In the functional study, contractile responses to noradrenaline were evaluated in human prostate and mesenteric artery. [3H]-PZ bound to human prostatic and aortic membranes with subnanomolar affinity. [3H]-KMD also bound to human prostate, with higher affinity than [3H]-PZ; whereas it did not bind sufficiently to human aorta. Competition of [3H]-PZ binding revealed that KMD-3213 had more than 200-fold higher affinity for human prostate than for aorta. Binding profiles of antagonists revealed that human prostate predominantly expressed α1A-AR, whereas human aorta

expressed α1B-AR mainly. In functional expts., KMD-3213 potently inhibited the noradrenaline-induced contraction in human prostate as potently as tamsulosin, although prazosin showed relatively low affinity. Comparing these functional affinities with those in the mesenteric artery, only KMD-3213 exhibited substantial tissue selectivity, showing more than 100-fold higher affinity for human prostate than for mesenteric artery. Functional affinity of each antagonist suggested that noradrenaline-induced contractions were mainly mediated by α1L-AR in the human prostate and by α1B-AR in the mesenteric artery. These results suggest that KMD-3213 is a substantially prostate-selective α1-AR antagonist in human tissues compared with other α1-AR antagonists.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:345446 CAPLUS
DOCUMENT NUMBER: 133:99703
TITLE: Cloning of rabbit α1b-adrenoceptor and pharmacological comparison of α1a-, α1b- and α1d-adrenoceptors in rabbit
AUTHOR(S): Piao, H.; Taniguchi, T.; Nakamura, S.; Zhu, J.; Suzuki, F.; Mikami, D.; Muramatsu, I.
CORPORATE SOURCE: School of Medicine, Department of Pharmacology, Fukui Medical University, Matsuoka, Fukui, 910-1193, Japan
SOURCE: European Journal of Pharmacology (**2000**), 396(1), 9-17
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have isolated a cDNA clone of the rabbit α1b-adrenoceptor which has an open reading frame of 1557 nucleotides encoding a protein of 518 amino acids. The sequence shows higher identity to those of hamster, human, and rat α1b-adrenoceptors than to those of rabbit α1a- and α1d-adrenoceptors. The pharmacol. binding properties of this clone expressed in Cos-7 cells showed a characteristic profile as α1b-adrenoceptor; high affinity for prazosin (pKi=10.3), relatively high affinity for tamsulosin (9.5) and low affinity for KMD 3213 (8.5), WB 4101 (8.7), and BMY 7378 (7.3). We have compared the levels of mRNA expression of three α1-adrenoceptor subtypes in rabbit tissues using the competitive reverse transcription/polymerase chain reaction (RT/PCR) assay. In most rabbit tissues except heart, α1a-adrenoceptor mRNA was expressed 10 folds more than the other two subtypes. However, binding expts. with [3H]prazosin and [3H]KMD 3213 in rabbit tissues revealed a poor relationship between binding d. and mRNA level. Especially, α1b binding sites were exclusively predominant in spleen, whereas the α1b subtype was minor at the mRNA level. These results indicate a high identity of structural and pharmacol. profiles of three distinct α1-adrenoceptor subtypes between rabbit and other species, but there are species differences in their distribution.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:309881 CAPLUS
DOCUMENT NUMBER: 133:69131
TITLE: Splice isoforms of α1a-adrenoceptor in rabbit
AUTHOR(S): Suzuki, Fumiko; Taniguchi, Takanobu; Takauji, Rumiko; Murata, Satoshi; Muramatsu, Ikunobu
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Fukui

Medical University, Fukui, 910-1193, Japan
SOURCE: British Journal of Pharmacology (2000), 129(8), 1569-1576
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two splice isoforms of rabbit α1a-adrenergic receptor (AR), (named α1a-OCU.2-AR and α1a-OCU.3-AR) have been isolated from the liver cDNA library in addition to the previously reported isoform (α1a-OCU.1-AR). Although they have the identical splice position with human α1a-AR isoforms, the C-terminal sequences are distinct from those of human isoforms. Among these rabbit α1a-AR isoforms, there are no significant differences in pharmacol. properties: high affinity for prazosin, WB 4101, KMD-3213 and YM 617 and low affinity for BMY 7378, using COS-7 cells expressing each isoform by radioligand binding assay. Competitive reverse transcription-polymerase chain reaction (RT-PCR) anal. revealed that mRNA of α1a-ARs was expressed in liver, thoracic aorta, brain stem and thalamus of rabbit. The splice isoforms exhibited a distinct distribution pattern in rabbit; α1a-OCU.1-AR was expressed most abundantly in those tissues. CHO clones, stably expressing each isoforms with receptor d. 740 fmol mg-1 protein in α1a-OCU.1-AR, 1200 fmol mg-1 in α1a-OCU.2-AR and 570 fmol mg-1 in α1a-OCU.3-AR, resp., showed a noradrenaline-induced increase in inositol trisphosphate which was suppressed by prazosin. Noradrenaline elicited a concentration-dependent increase in extracellular acidification rate (EAR) in the CHO clones with pEC50 values of 6.19 for α1a-OCU.1-AR, 6.49 for α1a-OCU.2-AR and 6.58 for α1a-OCU.3-AR, resp. Noradrenaline caused a concentration-dependent increase in intracellular Ca2+ concentration ([Ca2+]i) in the CHO clones with pEC50 values of 6.14 for α1a-OCU.1-AR, 7.25 for α1a-OCU.2-AR and 7.70 for α1a-OCU.3-AR, resp. In conclusion, the present study shows the occurrence of three splice isoforms of rabbit α1a-AR, which are unique in C-terminal sequence and in tissue distribution. They show similar pharmacol. profiles in binding studies but α1a-OCU.3-AR had the highest potency of noradrenaline in functional studies in spite of the lowest receptor d. These findings suggest that the structure of C-terminus of α1a-ARs may give the characteristic functional profile.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:125868 CAPLUS
DOCUMENT NUMBER: 132:245855

TITLE: Ligand design for α1-adrenoceptor subtype selective antagonists

AUTHOR(S): Bremner, John B.; Coban, Burak; Griffith, Renate; Groenewoud, Karina M.; Yates, Brian F.
CORPORATE SOURCE: Department of Chemistry, University of Wollongong, Wollongong, 2522, Australia

SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(1), 201-214
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB α1-Adrenoceptors have three subtypes and drugs interacting selectively with these subtypes could be useful in the treatment of a variety of diseases. In order to gain an insight into the structural

principles governing subtype selectivity, ligand based drug design (pharmacophore development) methods have been used to design a novel 1,2,3-thiadiazole ring D analog of the aporphine system. Synthesis and testing of this compound as a ligand on cloned and expressed human α1-adrenoceptors is described. Low binding affinity was found, possibly due to an unfavorable electrostatic potential distribution. Pharmacophore models for antagonists at the three adrenoceptor sites (α1A, α1B, α1D) were generated from a number of different training sets and their value for the design of new selective antagonists discussed. The first preliminary antagonist pharmacophore model for the α1D adrenoceptor subtype is also reported.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:632706 CAPLUS
DOCUMENT NUMBER: 131:317542
TITLE: KMD-3213, a uroselective and long-acting α1a-adrenoceptor antagonist, tested in a novel rat model
AUTHOR(S): Akiyama, Katsuyoshi; Hora, Masachiyo; Tatemichi, Satoshi; Masuda, Naoyuki; Nakamura, Syunji; Yamagishi, Ryoichi; Kitazawa, Makio
CORPORATE SOURCE: Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., Nagano, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1999**), 291(1), 81-91
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB KMD-3213, an α1a-adrenoceptor (AR) antagonist, is under development for the treatment of urinary outlet obstruction in patients with benign prostatic hypertrophy. In the present study, we developed a rat model to investigate simply the effects of α1-AR antagonists on the intraurethral pressure (IUP) response to phenylephrine. Using this model, inhibitory effects of both i.v. and intraduodenally administered KMD-3213 on the IUP response were evaluated and compared to those of other reference compds., including prazosin and tamsulosin. In addition, the hypotensive effects of these compds. were estimated to evaluate uroselectivity. I.v. administered α1-AR antagonists tested, including KMD-3213, potently inhibited the IUP response in a dose-dependent manner. Although the higher doses of those compds. almost completely inhibited the IUP response, yohimbine failed to inhibit the response. When the in vivo potencies of those compds. on IUP response were correlated with their affinities for the human or animal recombinant α1-AR subtypes, α1a-AR gave the best correlation. In this model, KMD-3213 had greater uroselectivity than any other compds. examined, by both i.v. and intraduodenal routes. Moreover, 12, 18, and 24 h after the oral administration of KMD-3213, a dose-dependent inhibition of the IUP response was found, whereas the effect of tamsulosin disappeared at 18 h after the oral administration. These data indicate that KMD-3213 is a highly uroselective α1-AR antagonist with a longer duration of action. In addition, this model is useful for not only estimation of uroselectivity but also some part of the administration, distribution, metabolism, and excretion of many compds. to discover uroselective compds.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:626075 CAPLUS
DOCUMENT NUMBER: 131:252591
TITLE: Combination of α1-adrenoceptor antagonists and endothelin antagonists for the treatment of benign prostatic hyperplasia
INVENTOR(S): Broten, Theodore P.; Siegl, Peter K. S.; Nichtberger, Steven A.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9948530	A1	19990930	WO 1999-US6014		19990319 <--
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 9930112	A1	19991018	AU 1999-30112		19990319 <--
US 6410554	B1	20020625	US 1999-274839		19990323 <--
PRIORITY APPLN. INFO.:			US 1998-79041P	P	19980323
			GB 1998-10895	A	19980520
			WO 1999-US6014	W	19990319

AB A pharmaceutical composition for the treatment of benign prostatic hyperplasia comprises an α1a-adrenoceptor antagonist, a non-selective endothelin antagonist, and optionally a 5α-reductase inhibitor. The combination therapy improves lower urinary tract symptoms including increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia or symptomatic prostatism. The efficacy of endothelin antagonists and α1a-adrenoceptor antagonists for inhibition of ET-1 and α1-adrenoceptor-mediated prosthatic urethral contractions was tested in a mongrel dog model. The preparation of the α1a-adrenoceptor antagonist trans-(+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid [3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl]amide is presented.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

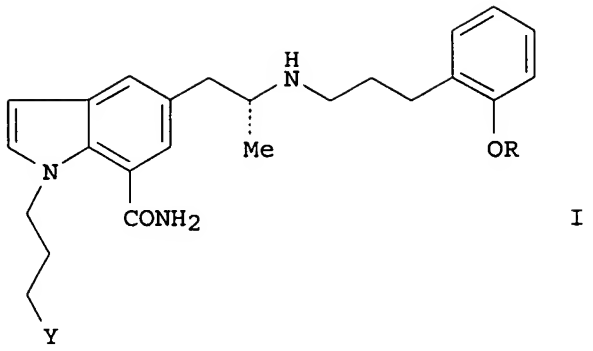
L4 ANSWER 29 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:584010 CAPLUS
DOCUMENT NUMBER: 132:117331
TITLE: Human α1-adrenoceptor subtypes: identification of selective antagonists and their interactions with quinidine and verapamil
AUTHOR(S): Shibata, Katsushi
CORPORATE SOURCE: School of Medicine, Keio University, Japan
SOURCE: Keio Igaku (**1999**), 76(4), T301-T311
CODEN: KEIGAS; ISSN: 0368-5179
PUBLISHER: Keio Igakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB KMD 3213 had selective antagonist activity on human α1a-adrenoceptor subtype, with synergistic interactions with quinidine or verapamil.

L4 ANSWER 30 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:566024 CAPLUS
DOCUMENT NUMBER: 131:184863
TITLE: Preparation of (R)-5-[2-[(2-phenoxyethyl)amino]propyl]indole-7-carboxamide derivatives as α1-adrenaline receptor blockers
INVENTOR(S): Kitazawa, Makio; Yamaguchi, Toshiaki; Miyata, Hiroshi; Ajisawa, Yukiyoshi
PATENT ASSIGNEE(S): Kissei Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 9943652	A1	19990902	WO 1999-JP732		19990219	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM						
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
CA 2321547	AA	19990902	CA 1999-2321547		19990219	<--
AU 9925478	A1	19990915	AU 1999-25478		19990219	<--
AU 766088	B2	20031009				
BR 9908301	A	20001031	BR 1999-8301		19990219	<--
EP 1057813	A1	20001206	EP 1999-905242		19990219	<--
EP 1057813	B1	20040421				
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, FI, RO						
RU 2212404	C2	20030920	RU 2000-122435		19990219	<--
AT 264841	E	20040515	AT 1999-905242		19990219	
ES 2220043	T3	20041201	ES 1999-905242		19990219	
NZ 506497	A	20041224	NZ 1999-506497		19990219	
ZA 9901590	A	19990827	ZA 1999-1590		19990226	<--
NO 2000004277	A	20000911	NO 2000-4277		20000825	<--
NO 317257	B1	20040927				
US 6310086	B1	20011030	US 2000-622871		20001023	<--
HK 1036974	A1	20041224	HK 2001-106719		20010924	
PRIORITY APPLN. INFO.:			JP 1998-90572	A	19980227	
			WO 1999-JP732	W	19990219	

OTHER SOURCE(S): MARPAT 131:184863
GI



I

AB Indole derivs. represented by general formula [(R)-I] or pharmacol. acceptable salts thereof (R represents Et or 2,2,2-trifluoroethyl; Y represents hydroxy or pivaloyloxy) are prepared These compds. have a remarkable and long-lasting effect of lowering ocular pressure, since they are slowly excreted once they are transferred inside the eyes. They are also reduced in side effects such as lowering blood pressure (hypotension) and orthostatic anemia, and thus are useful as drugs for treatment or prevention of high ocular pressure and cataract. Thus, tert-Bu (R)-N-[2-[7-carbamoyl-1-(3-hydroxypropyl)-2,3-dihydro-1H-indol-5-yl]-1-methylethyl]-N-[2-(2-ethoxyphenoxy)ethyl]carbamate was refluxed with ammonium formate in the presence of 10% Pd-C in MeOH for 36 h to give tert-Bu (R)-N-[2-[7-carbamoyl-1-(3-hydroxypropyl)-1H-indol-5-yl]-1-methylethyl]-N-[2-(2-ethoxyphenoxy)ethyl]carbamate which was treated with concentrated HCl under ice-cooling and stirred at room temperature for 3 h to give the title compound (I; Y = OH, R = Et). I.HCl (Y = OH, R = Et) in vitro showed IC50 of 2.7 μM for inhibiting the norepinephrine-induced contraction of rat seminal canal.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:393863 CAPLUS
DOCUMENT NUMBER: 131:208437
TITLE: KMD-3213 Kissei Pharmaceutical Co Ltd
AUTHOR(S): Kamali, Farhad
CORPORATE SOURCE: Wolfson Unit of Clinical Pharmacology, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, NE1 7RU, UK
SOURCE: Current Opinion in Central & Peripheral Nervous System Investigational Drugs (**1999**), 1(2), 248-252
CODEN: COCDFA; ISSN: 1464-844X
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 36 refs. KMD-3213, an α1 adrenoceptor antagonist from Kissei, is in phase II clin. trials in Japan for the potential treatment of dysuria associated with benign prostatic hyperplasia (BPH). This compound is a potent and highly-selective antagonist to prostatic receptors and therefore may not produce the side-effects associated with other α1 antagonists. Phase I trials have begun in the UK with KMD-3213 for this indication.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:385955 CAPLUS
DOCUMENT NUMBER: 131:139836
TITLE: Characterization of α1-adrenoceptors expressed in a novel vascular smooth muscle cell line cloned from p53 knockout mice, P53LMAC01 (AC01) cells
AUTHOR(S): Ohmi, Kazuhiro; Shinoura, Hitomi; Nakayama, Yasuhisa; Goda, Nobuhito; Tsujimoto, Gozoh
CORPORATE SOURCE: Department of Pathology, National Children's Medical Research Center, Tokyo, 154-8509, Japan
SOURCE: British Journal of Pharmacology (1999), 127(3), 756-762
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We pharmacol. studied the α1-adrenoceptor (AR) subtype(s) involved in receptor-mediated signaling in a novel vascular smooth muscle cell line cloned from p53 knockout mice, P53LMAC01 (AC01) cells. Radioligand binding studies with [125I]-HEAT showed the existence of a homogeneous population of binding site with an affinity (Kd value) of 0.4 nM and a maximum number of binding sites (Bmax) of 100 fmol mg-1 protein. Catecholamines competed for [125I]-HEAT binding stereospecifically and with the characteristic α1-AR potency series. Displacement curves for BMY-7378 and KMD-3213 best fitted a one-site model with a pKi value (-log10 (equilibrium inhibition constant)) of 6.06 and 7.07, resp. Reverse transcription-polymerase chain reaction (RT-PCR) assay detected α1B- and α1D-AR, but not α1A-AR transcript. Chlorethylclonidine (CEC) treatment nearly abolished (-)noradrenaline (NA) (10 μM)-induced inositol[1,4,5]trisphosphate (IP3) production, and BMY-7378 inhibited the response with a Ki value of 0.3 nM, which value was similar to that obtained in the cells expressing α1D-AR. In both AC01 cells and cells expressing α1D-AR, BMY-7378 protected α1-ARs from CEC alkylation while it had little protective effect on CEC alkylation and NA-induced IP3 production in cells expressing α1B-AR. The results indicate that AC01 cells contain predominantly α1B-ARs and a small population of α1D-ARs; however, phosphoinositide (PI)/Ca2+ signaling is mainly mediated through the minor population of α1D-ARs, rather than the α1B-ARs.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:305630 CAPLUS
DOCUMENT NUMBER: 131:97473
TITLE: Pharmacological analysis of the novel, selective α1-adrenoceptor antagonist, KMD-3213, and its suitability as a tritiated radioligand
AUTHOR(S): Murata, Satoshi; Taniguchi, Takanobu; Muramatsu, Ikunobu
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Fukui Medical University, Fukui, 910-1193, Japan
SOURCE: British Journal of Pharmacology (1999), 127(1), 19-26
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pharmacol. profiles of tritiated KMD-3213, a new antagonist of

α1-adrenoceptor (AR), were examined in recombinant and native α1-AR, and compared with those of prazosin (PZ) and tamsulosin (YM-617). In saturation expts., [3H]-KMD (10 - 2000 pM) showed high affinity for α1a-AR (pKD=10.5). However, no significant binding to α1b-AR and insufficient/unsatd. binding to α1d-AR were observed at concns. up to 2000 pM. In contrast, [3H]-PZ and [3H]-YM bound to all subtypes with high affinity (pKD>9). In competition expts., KMD-3213 also had higher affinity for α1a-AR than for other two subtypes; pKi = 10.4, 8.1 and 8.6 for α1a-, α1b- and α1d-AR, resp. [3H]-KMD also bound to the native α1A-AR (rat submaxillary gland) with high affinity, but not to α1B-AR (rat liver). In rat kidney which expresses α1A- and α1B-AR, [3H]-KMD and [3H]-PZ bound to a single high-affinity site (pKD = 10.8 and 10.1, resp.) with distinct amount of bindings sites (Bmax = 159 and 267 fmol mg-1 protein, resp.). [3H]-PZ binding sites consisted of low- and high-affinity sites for KMD-3213 (pKi = 7.6 and 10.7, resp.), for WB4101 (pKi = 8.1 and 10.0) and for YM-617 (pKi = 8.7 and 10.8). The proportion of the high affinity site was approx. 60% in these drugs which was compatible to the ratio between Bmax of [3H]-KMD and [3H]-PZ. [3H]-KMD binding sites consisted of a single site for these drugs with affinities which were similar to those of the high affinity sites in [3H]-PZ binding. In functional expts., KMD-3213 antagonized the contractile responses to NS-49 or noradrenaline (NA) with higher affinity in functional α1A- (rat caudal artery, pA2 = 10.0 against NS-49) and α1L-AR (dog mesenteric artery, pA2 = 9.9 against NA) than in α1B- (dog carotid artery, pA2 = 7.7 against NA) and α1D-AR (rat thoracic aorta, pA2 = 8.3 against NA). These results confirm the α1A-AR selectivity and high affinity of KMD-3213, and indicate that [3H]-KMD can label selectivity α1A-AR.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:222860 CAPLUS
DOCUMENT NUMBER: 130:232518
TITLE: Remedies for dysuria resulting from prostatic hypertrophy
INVENTOR(S): Muramatsu, Ikunobu; Murata, Satoshi; Akiyama, Katsuyoshi; Kojima, Masami
PATENT ASSIGNEE(S): Kissei Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9915202	A1	19990401	WO 1998-JP4234		19980921 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 9890959	A1	19990412	AU 1998-90959		19980921 <--
PRIORITY APPLN. INFO.:			JP 1997-296135	A	19970922
			WO 1998-JP4234	W	19980921

AB Remedies for dysuria resulting from prostatic hypertrophy, contain a highly selective α1L-adrenergic receptor blocker as the active ingredient and do not affect blood pressure. The remedies are prepared in a conventional manner through the incorporation of an effective amount of (-)-(R)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide, a pharmacol. acceptable salt thereof, or a solvate of either; or alternatively, (-)-(R)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indole-7-carboxamide, a pharmacol. acceptable salt thereof, or a solvate of either.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:233317 CAPLUS

DOCUMENT NUMBER: 129:239

TITLE: In vivo receptor binding of novel α1-adrenoceptor antagonists for treatment of benign prostatic hyperplasia

AUTHOR(S): Yamada, Shizuo; Ohkura, Takashi; Kimura, Ryohei; Kawabe, Kazuki

CORPORATE SOURCE: Department of Biopharmacy, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, 422, Japan

SOURCE: Life Sciences (**1998**), 62(17/18), 1585-1589
CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB New types of α1-adrenoceptor antagonists (tamsulosin, KMD-3213 and JTH-601) are currently receiving a great deal of attention, especially in terms of developing effective therapeutic agents to treat bladder outlet obstruction with less side effects, such as postural hypotension, in patients with benign prostatic hyperplasia (BPH). In vivo α1-adrenoceptor binding properties of these antagonists in prostate and other tissues of rats were examined I.v. injections of tamsulosin, KMD-3213 and JTH-601 inhibited dose-dependently in vivo specific [3H]tamsulosin binding in various tissues. Ratios of ID50(aorta) to ID50(prostate) of KMD-3213 and JTH-601 were greater than those of tamsulosin and prazosin. Further, the ratios of ID50(spleen) to ID50(submaxillary gland) of these drugs were greater than that of prazosin. Following i.v. injections of [3H]KMD-3213 in rats, the amount of specific binding in prostate was significantly greater than that of [3H]prazosin, but that in aorta or spleen was much smaller. Interestingly, [3H]JTH-601 showed little in vivo specific binding in aorta. These data suggest that KMD-3213 and JTH-601 exhibit higher affinity to α1-adrenoceptors in prostate and submaxillary gland than in vascular tissues in vivo.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 36 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:420276 CAPLUS

DOCUMENT NUMBER: 127:130827

TITLE: KMD-3213, a novel α1A-adrenoceptor antagonist, potently inhibits the functional α1-adrenoceptor in human prostate

AUTHOR(S): Moriyama, Nobuo; Akiyama, Katsuyoshi; Murata, Satoshi; Taniguchi, Jun; Ishida, Norio; Yamazaki, Satoru; Kawabe, Kazuki

CORPORATE SOURCE: Department of Urology, Faculty of Medicine, The

University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan
SOURCE: European Journal of Pharmacology (1997), 331(1), 39-42
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB KMD-3213, (-)-(R)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide, is a novel and selective α1A-adrenoceptor antagonist. The potency of this drug to antagonize functional α1-adrenoceptor-mediated contraction in human prostatic smooth muscle was evaluated and compared with that of other α1-adrenoceptor antagonists. KMD-3213 inhibited noradrenaline-induced contractions with an apparent pKB value of 9.45, indicating a potency similar to that of tamsulosin. The affinity of prazosin for prostatic α1-adrenoceptors is given as potency for the α1L-adrenoceptor with an estimated pA2 value of 8.84. The data obtained in this study suggest that KMD-3213, an α1A-adrenoceptor-selective antagonist, has strong affinity for the α1L-adrenoceptor in the human prostate.

L4 ANSWER 37 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:50390 CAPLUS
DOCUMENT NUMBER: 126:166082
TITLE: Pharmacophore development for antagonists at α1 adrenergic receptor subtypes
AUTHOR(S): Bremner, J.B.; Coban, B.; Griffith, R.
CORPORATE SOURCE: Department of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia
SOURCE: Journal of Computer-Aided Molecular Design (1996), 10(6), 545-557
CODEN: JCADEQ; ISSN: 0920-654X
PUBLISHER: ESCOM
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Many receptors, including α1-adrenergic receptors, have a range of subtypes. This offers possibilities for the development of highly selective antagonists with potentially fewer detrimental effects. Antagonists developed for α1A receptors, for example, would have potential in the treatment of benign prostatic hyperplasia. As part of the mol. design process, structural features necessary for the selective affinity for α1A and α1B adrenergic receptors have been investigated. The mol. modeling software (particularly the Apex module) of Mol. Simulations, Inc. was used to develop pharmacophore models for these two subtypes. Low-energy conformations of a set of known antagonists were used as input, together with a classification of the receptor affinity data. The biophores proposed by the program were evaluated and pharmacophores were proposed. The pharmacophore models were validated by testing the fit of known antagonists, not included in the training set. The critical structural feature for selectivity between the α1A and α1B adrenergic receptor sites is the distance between the basic nitrogen atom and the center of an aromatic ring system. This will be exploited in the design and synthesis of structurally new selective antagonists for these sites.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:711990 CAPLUS

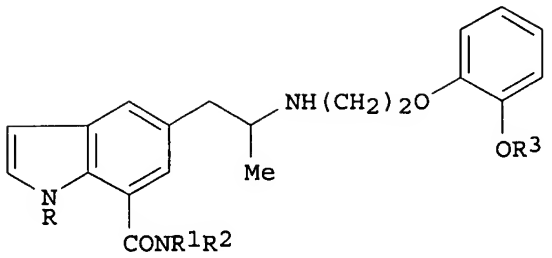
DOCUMENT NUMBER: 126:26680
TITLE: Effect of KMD-3213, an α1a-adrenoceptor-selective antagonist, on the contractions of rabbit prostate and rabbit and rat aorta
AUTHOR(S): Yamagishi, Ryoichi; Akiyama, Katsuyoshi; Nakamura, Shunji; Hora, Masachiyo; Masuda, Naoyuki; Matsuzawa, Akane; Murata, Satoshi; Ujiie, Arao; Kurashina, Yoshikazu; et al.
CORPORATE SOURCE: Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., 4365-1, Kashiwabara, Hotaka, Nagano, Japan
SOURCE: European Journal of Pharmacology (**1996**), 315(1), 73-79
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB KMD-3213, (-)-(R)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide, a newly synthesized α1-adrenoceptor antagonist, has been shown to have potent action toward, and to be selective for human cloned and native α1-adrenoceptors. In the present study, we characterized the inhibitory effect of KMD-3213 on the phenylephrine (α1-adrenoceptor-selective agonist)-induced contraction of rabbit prostate, rabbit thoracic aorta and rat thoracic aorta to functionally confirm the tissue selectivity of KMD-3213. The mean pA2 value for KMD-3213 for the inhibition of the rabbit prostatic contraction was 10.05, whereas the values for the rabbit and rat aortic contractions were 9.36 and 8.13, resp. The order of mean pA2 values for the inhibition of the rabbit prostatic contraction was KMD-3213≥tamsulosin>>prazosin, whereas that for the rabbit and rat aortic contractions was tamsulosin>KMD-3213>prazosin and tamsulosin≥prazosin>>KMD-3213, resp. KMD-3213 produced a sigmoidal inhibition curve for single-dose phenylephrine-induced contractions of rabbit prostate, whereas it produced a non-sigmoidal curve for that of rabbit aorta. KMD-3213 had no effect on isoproterenol-induced chronotropic action in guinea-pig atria, and 5-hydroxytryptamine-, histamine- and acetylcholine-mediated contractions of rabbit aorta. These results indicate that the potency of the inhibitory activity of KMD-3213 depends on the tissue subtype expression and that KMD-3213 preferentially antagonizes prostatic contraction.

L4 ANSWER 39 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:259454 CAPLUS
DOCUMENT NUMBER: 124:316982
TITLE: Preparation of indole derivatives for treatment of dysuria
INVENTOR(S): Kitazawa, Makio; Saka, Masaaki; Okazaki, Kosuke; Ozawa, Motohiro; Yazaki, Toshikazu; Yamagishi, Ryoichi
PATENT ASSIGNEE(S): Kissei Pharmaceutical, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 29 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07330726	A2	19951219	JP 1994-143904	19940601 <--
JP 3331048	B2	20021007		
PRIORITY APPLN. INFO.:			JP 1994-143904	19940601

OTHER SOURCE(S): MARPAT 124:316982
GI



I

AB The title compds. I [R = aliphatic acyl, etc.; R1, R2 = H, alkyl; a proviso is given; R3 = (halo-substituted) alkyl] are prepared (R)-1-(3-Hydroxypropyl)-5-[2-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino]propyl]indole-7-carboxamide (II) (preparation given) showed ED50 of 1.8 μg/Kg against phenylephrine-induced contraction of urinary tract in rats, vs. ED50 of 4 μg/Kg for prazosin. II at 18 μg/kg decreased blood pressure by 10% in rats.

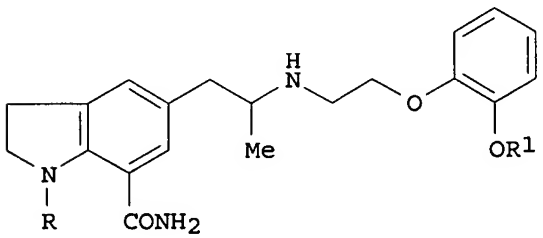
L4 ANSWER 40 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:786212 CAPLUS
DOCUMENT NUMBER: 123:246611
TITLE: KMD-3213, a novel, potent, α1a-adrenoceptor-selective antagonist: characterization using recombinant human α1-adrenoceptors and native tissues
AUTHOR(S): Shibata, Katsushi; Foglar, Rudolf; Horie, Kuniko; Obika, Kenji; Sakamoto, Aiji; Ogawa, Satoshi; Tsujimoto, Gozoh
CORPORATE SOURCE: Dep. Mol. and Cell Pharmacology, Natl. Children's Med. Res. Cent., Tokyo, 154, Japan
SOURCE: Molecular Pharmacology (**1995**), 48(2), 250-8
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB α1-Adrenoceptors (ARs) comprise a heterogeneous family, and subtype-selective ligands are valuable for studying the functional role of each receptor subtype. We characterized a newly synthesized, α1-AR antagonist, KMD-3213, by using Chinese hamster ovary cells stably expressing the three cloned human α1-ARs (α1a, α1b, and α1d), as well as native rat and human tissues. KMD-3213 potently inhibited 2-[2-(4-hydroxy-3-[125I]iodophenyl)ethylaminomethyl]-α-tetralone binding to the cloned human α1a-AR, with a Ki value of 0.036 nM, but had 583- and 56-fold lower potency at the α1b- and α1d-ARs, resp. KMD-3213 inhibited norepinephrine-induced increases in intracellular Ca2+ concns. in α1a-AR-expressing Chinese hamster ovary cells with an IC50 of0.32 nM but had a much weaker inhibitory effect on the α1b- and α1d-ARs. Using pharmacol. well characterized native at tissues [submaxillary gland (α1A-AR-expressing tissue), liver (α1B-AR-expressing tissue), and heart (mixed α1A- and α1B-AR-expressing tissue)], binding studies showed that inhibition curves for KMD-3213 in submaxillary gland and liver best fit a one-site

model (with Ki values of 0.15 and 16 nM, resp.), whereas KMD-3213 had high and low affinity sites in heart membranes. Chloroethylclonidine treatment of rat heart membranes completely eliminated the low affinity sites for KMD-3213. Furthermore, in human liver and prostate KMD-3213 could identify high and low affinity sites, the Ki values of which corresponded well to those for the cloned human α1a- and α1b-ARs, resp. Moreover, the affinity of KMD-3213 was found to be approx. 10-fold higher at the cloned human α1a-AR than at the cloned rat α1a-AR. KMD-3213 is a potent and highly selective antagonist for the human α1a-AR and would be useful for studying the physiol. roles of human α1-AR subtypes.

L4 ANSWER 41 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:358647 CAPLUS
DOCUMENT NUMBER: 123:111846
TITLE: Indoline compounds for the treatment of dysuria.
INVENTOR(S): Kitazawa, Makio; Ban, Masaaki; Okazaki, Kosuke; Ozawa, Motoyasu; Yazaki, Toshikazu; Yamagishi, Ryoichi
PATENT ASSIGNEE(S): Kissei Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 75 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 600675	A1	19940608	EP 1993-309450	19931126 <--
EP 600675	B1	19980708		
R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
CA 2110454	AA	19940603	CA 1993-2110454	19931201 <--
CA 2110454	C	20051025		
JP 06220015	A2	19940809	JP 1993-342177	19931201 <--
JP 2944402	B2	19990906		
US 5387603	A	19950207	US 1993-159624	19931201 <--
JP 11269117	A2	19991005	JP 1998-377981	19981216 <--
JP 3552935	B2	20040811		
PRIORITY APPLN. INFO.:			JP 1992-356197 A	19921202
			JP 1993-342177 A3	19931201

OTHER SOURCE(S): MARPAT 123:111846
GI



I

AB Indoline compds. I (R = saturated or unsatd. acyl group; R1 = alkyl, haloalkyl, etc.) were disclosed. I and pharmaceutically acceptable salts thereof, exhibit a selective suppressive action on urethral contraction, and thus are useful as therapeutic agents for the treatment of dysuria with less hypertension including postural hypotension. A specifically

claimed example compound is I (R = 1-oxobutyl; R1 = CH2CF3). However, pharmacol. test data for I were not reported.

=> l3 and crystal
L5 1 L3 AND CRYSTAL

=> d l5

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:220314 CAPLUS
DN 140:259125
TI **Crystal** for oral solid drug and oral solid drug for dysuria treatment containing the same
IN Tsuru, Eiji; Toda, Michio; Hirata, Kazuma
PA Kissei Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004022538	A1	20040318	WO 2003-JP11345	20030905
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2496780	AA	20040318	CA 2003-2496780	20030905
	EP 1541554	A1	20050615	EP 2003-794249	20030905
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	BR 2003014338	A	20050705	BR 2003-14338	20030905
	NO 2005001709	A	20050606	NO 2005-1709	20050406
PRAI	JP 2002-262157	A	20020906		
	WO 2003-JP11345	W	20030905		

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:220314 CAPLUS
DOCUMENT NUMBER: 140:259125
TITLE: **Crystal** for oral solid drug and oral solid drug for dysuria treatment containing the same
INVENTOR(S): Tsuru, Eiji; Toda, Michio; Hirata, Kazuma
PATENT ASSIGNEE(S): Kissei Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022538	A1	20040318	WO 2003-JP11345	20030905
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2496780	AA	20040318	CA 2003-2496780	20030905
EP 1541554	A1	20050615	EP 2003-794249	20030905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003014338	A	20050705	BR 2003-14338	20030905
NO 2005001709	A	20050606	NO 2005-1709	20050406
PRIORITY APPLN. INFO.:			JP 2002-262157 A	20020906
			WO 2003-JP11345 W	20030905

AB A **crystal** for oral solid drug comprised of indoline compound (KMD-3213) which exerts α1-adrenaline receptor shielding activity, is useful as a therapeutic agent for dysuria, wherein in the powder X-ray diffraction pattern, the compound is characterized by main peaks of 5.5°± 0.2°, 6.1°± 0.2°, 9.8°± 0.2°, 11.1°± 0.2°, 12.2°± 0.2°, 16.4°± 0.2°, 19.7°± 0.2° and 20.0°± 0.2° as 2θ. There is further provided an oral solid drug for dysuria treatment containing the **crystal** as an active ingredient. An α- **crystal** of KMD-3213 was prepared, and its stability was examined A capsule containing KMD-3213 α- **crystal** 2 mg/capsule was formulated.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> l3 and polymorph
L6 0 L3 AND POLYMORPH

=> d his

(FILE 'HOME' ENTERED AT 15:17:28 ON 23 JAN 2006)

FILE 'REGISTRY' ENTERED AT 15:17:50 ON 23 JAN 2006
L1 2 KMD-3213

FILE 'CAPLUS, MEDLINE' ENTERED AT 15:20:41 ON 23 JAN 2006
L2 61 L1
L3 61 DUP REM L2 (0 DUPLICATES REMOVED)
L4 41 L3 AND PY<2004
L5 1 L3 AND CRYSTAL
L6 0 L3 AND POLYMORPH

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	129.44	141.37

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-31.50	-31.50

STN INTERNATIONAL LOGOFF AT 15:30:48 ON 23 JAN 2006